

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
16 October 2003 (16.10.2003)

PCT

(10) International Publication Number
WO 03/085138 A1

(51) International Patent Classification⁷: **C12Q 1/70, A61K 39/23**

(21) International Application Number: **PCT/US03/09269**

(22) International Filing Date: **27 March 2003 (27.03.2003)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
60/368,654 29 March 2002 (29.03.2002) US

(71) Applicant (for all designated States except US): **MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).**

(72) Inventors; and

(75) Inventors/Applicants (for US only): **XIE, Liangzhi [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). GOOCHEE, Charles, F. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).**

(74) Common Representative: **MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).**

(81) Designated States (national): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.**

(84) Designated States (regional): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).**

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **METHODS OF VIRUS PRODUCTION**

(57) Abstract: A simple yet effective method of increasing production of a thermo-stable virus, such as adenovirus and picornavirus, is presented. The method entails a temperature shift strategy whereby the culture of host cells are shifted to a sub-optimal temperature for a period of time prior to virus infection or cells are grown at a sub-optimal level for the entire cell expansion process including one or more than one passages of cell growth from cryopreserved cells, followed by a shift back to a more optimal temperature at or near the time of virus infection of the respective host cells. Adaptation of such a temperature shift strategy present a simple yet effective method to substantially increase recoverable virus within a respective host cell/virus production scheme without the need to further manipulate other culture and/or media conditions within an established host cell / virus production scheme.

509, 293



WO 03/085138 A1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/09269

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/70; A61K 39/23

US CL : 435/5, 235.1; 424/233.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/5, 235.1; 424/233.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	US 3,962,424 (ZYGRAICH et al) 08 June 1976 (08.06.1976), abstract and column 3, lines 15-29.	1-15

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

27 June 2003 (27.06.2003)

Date of mailing of the international search report

13 AUG 2003

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Valerie Bell-Harris for
Stacy B. Chen

Telephone No. 703-308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/09269

Continuation of B. FIELDS SEARCHED Item 3:

EAST, CAS ONLINE, MEDLINE, BIOSIS, EMBASE, CAPLUS, SCISEARCH

search terms: xie, goochee, adenovirus, cell culture, low, temperature, sub-optimum, harvest, purify